REMARKS

There is some ambiguity in the Office Action about whether the outstanding Office Action is final. The coversheet indicates the action is non-final, whereas several paragraphs in the concluding remarks indicate that the action is final. Applicant confirmed with Examiner Katcheves in a teleconference on May 31, 2005, that the Office Action mailed December 23, 2004 is a non-final Office Action. Applicant thanks the Examiner for this clarification.

Claims 1-32, 34-37, 42-45, and 75 are pending in the above-referenced application. The Examiner has rejected claims 1-32, 34-37, 42-45, and 75. Claims 1, 14, 30, 31, 32, and 42-45 are amended in this Response; and claims 4, 5, 6, 34, and 35 have been canceled. No new claims have been added. Applicant respectfully submits that no new matter is presented with these amendments. Applicant reserves the right to prosecute without prejudice in a future application subject matter amended from the claims by the Amendment submitted herewith. Applicant respectfully requests consideration of the amended claims presented herein and respectfully submits that the amended claims are now in condition for allowance.

I. Rejections under 35 U.S.C. § 102. The Examiner has rejected claims 1, 3, 4, 6-11, 13, 15-18, 20, 22-29, 30, 36-37, 43-45, and 75 under 35 U.S.C. § 102(b), as being anticipated by Roberts *et al.* (U.S. Patent 5,958,769, issued September 28, 1999). The Examiner maintains that Roberts *et al.* discloses a method for increasing the proliferation of various cells by administering inhibitors of p27 cyclin dependent kinase and that this method can be used on stem cells, progenitor cells, fibroblasts, myeloblasts, neurons, epithelial cells, hematopoietic progenitor cells, granulopoietic cells, and embryogenic cells. In addition, the Examiner maintains that Roberts *et al.* discloses that p27 inhibitors may be used with antagonists of p21 to increase the proportion of proliferating cells in a population. Applicant disagrees that Roberts *et al.* anticipates the claimed invention, because at best Roberts *et al.* merely suggests without any enabling support that a *combination* of p27 and p21 inhibitors might be used to increase the proportion of proliferating cells in a cell population (column 8, lines 19-29).

In response to the Applicant's arguments which were submitted in the last Response on August 13, 2004, the Examiner has suggested that "the test for 'enabling disclosure' is whether the public was in possession of the claimed invention before the date of the invention. See

MPEP 2121.01" The Examiner continues by quoting from the MPEP which cites *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985): "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." The answer to the questions whether the public was in possession of the claimed invention before the date of the invention or if one of ordinary skill in the art could have combined the publication's description with his or her own knowledge to make the claimed invention is an emphatic "No." Roberts *et al.* merely suggests the inhibition of p21 and p27 to increase the proportion of proliferating cells in a cells population. There is no evidence that such a combination was tried by Roberts *et al.* or for that matter any indication that such a combination would yield the desired results. Roberts *et al.* focuses only on the inhibition of p27 and merely suggests combining the inhibition of p27 with the inhibition of other mitotic inhibitors. However, solely in order to further prosecution Applicant has amended the claims rendering this rejection moot.

Claim 1 has been amended to recite a method of inhibiting only p21 activity in the cell and not inhibiting p27 activity. Since Roberts *et al.* does not teach inhibiting p21 alone, Roberts *et al.* cannot anticipate claim 1 or its dependencies. Claim 30 has been amended to recite a cell with less than wild type p21 activity but with wild type p27 activity. Again, Roberts *et al.* cannot anticipate claim 30 or its dependencies.

Applicant, therefore, requests that this rejection be removed.

II. **Rejections under 35 U.S.C. § 103.** The Examiner has rejected claims 1-32, 34-37, 42-45, and 75 under 35 U.S.C. § 103(a) as being unpatentable over Roberts *et al.* as applied to claims 1, 3, 4, 6-11, 13, 15-18, 20-22, 29, 30, 33, 36-41, 43-45, and 75, and further in view of Waldman *et al.* (*Cancer Research* 55:5187-90, 1995). The Examiner maintains that it would have been obvious to combine the teachings of Roberts *et al.* and Waldman *et al.* to increase the proliferation of cells by disrupting both p21 and p27 in a cell population. Applicant disagrees because the references even when combined fail to teach or suggest certain features of the claimed invention. Furthermore, even if the references could be combined to support an argument that it would be obvious to try to achieve the claimed invention, there still would be no reasonable expectation of success in achieving the desired result.

As amended, the present application claims the inhibition of p21 alone to increase the proportion of proliferating cells in a population. The teachings of Roberts *et al.* are described more fully above. In sum, Roberts *et al.* does not teach the inhibition or disruption of p21 alone; therefore, the Examiner relies on the teaching of Waldman *et al.* The Examiner states that Waldman *et al.* teaches the disruption of the p21 genes in human colorectal cancer cell line HCT-116. Neither reference alone teaches the inhibition or disruption of p21 alone in progenitor or stem cells.

In addition, there is no teaching or suggestion in either Roberts *et al.* or Waldman *et al.* that one might trying inhibiting p21 alone in stem or progenitor cells. The Examiner also does not provide any motivation for combining these two references. Therefore, the Examiner has not established a *prima facie* case of obviousness.

Furthermore, even if there were a suggestion or motivation to combine Roberts *et al.* and Waldman *et al.*, the combination could not render obvious the present claims to methods of expanding a population of cells by inhibiting p21 alone given the lack of a reasonable expectation of success in achieving the desired result. As discussed in the last two Responses, Waldman *et al.* only teaches the use of a fully differentiated cancer cell line. Waldman *et al.* does not teach or suggest any method involving the use of stem or progenitor cells. The claimed invention recites stem and progenitor cells. One cannot readily extrapolate the results in fully differentiated cancer cells to undifferentiated, pluripotent cells such as stem and progenitor cells. Although the studies of Roberts *et al.* were conducted in progenitor cells, Roberts *et al.* did not disrupt or inhibit p21 in any cells lines. Therefore, neither Roberts *et al.* nor Waldman *et al.* ever disrupted or inhibited p21 alone in a single stem or progenitor cell. The effect of cyclin-dependent inhibitor activity is unique and varies from cell to cell (*e.g.*, stem cells versus progenitor cells versus fully differentiated cells). Without such experimentation in stem or progenitor cells, there is no reasonable expectation of success in achieving the desired result of expanding a cell population. Therefore, without a reasonable expectation of success the *prima facie* case for obviousness has not been established, and Applicant requests that the rejection be removed.

III. **Rejections under 35 U.S.C. § 112, first paragraph.** Claims 27 and 75 stand rejected

under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Examiner maintains that the Specification is not enabling for antisense agents. Applicant maintains that the use of antisense agents is enabled given the working example on pages 44-51 of the Specification. In Example 3, a lentiviral vector was used to deliver a p21 antisense agent into hematopoietic cells. The transfected cells were then shown to have decreased levels of p21 activity, and a decreased proportion of the cells in G_0 of the cell cycle was observed. Human cells transduced with a p21-antisense vector were also used to transplant irradiated NOD/SCID mice. The treatment of cells with a p21-antisense vector was found to enhance the number of stem cells, while treatment with a control vector yielded minimal engraftment. These results demonstrate the use of antisense agents in accordance with the claimed invention. For claims 27 and 75 with respect to claim 3, in which p21 alone is inhibited, these experiments are directly applicable.

In addition, the Examiner has requested that Applicant submit a Declaration as evidence that the claimed invention is enabled. The Examiner is directed to the Declaration submitted herewith which describes results in a recent manuscript prepared by Dr. Scadden, an inventor on the present application, and others. The manuscript was accepted on March 17, 2005 for publication in *Gene Therapy*, a peer-reviewed journal, and is currently in press. The manuscript describes the transient reduction of p21 levels in hematopoietic stem/progenitor cells and megakaryoblastic cells treated with two specific RNAi constructs targeting p21. Both constructs knocked down p21 expression by 95-98%. Synthesized siRNA knocked down p21 expression for 10-15 days while the effect of transcribed shRNA lasted for 22-28 days. Given the successful results of inhibiting p21 activity using RNAi constructs as supported by the Declaration filed herewith, Applicant submits that claim 27 and 75 were enabled as of the filing date of the present application because based on the teaching of the Specification and the state of the art at the time of filing with regard to p21 and anti-sense agents one of ordinary skill in this art could use RNAi technology to inhibit the p21 activity in a cell. Applicant, therefore, submits that claims 27 and 75 are enabled and requests that the rejection be removed.

If it is believed that a telephone conversation would expedite matters, the Examiner is

invited to contact the undersigned at (617) 248-5215. Although it is believed that there is no fee associated with this amendment, if Applicant is mistaken, please charge any fees to our Deposit Account Number: 03-1721.

Respectfully submitted,

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I certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

June 22, 2005
Date

Signature

Kenneth R. Maben
Typed or Printed Name of person signing certificate

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